The description and prediction of antihypertensive drug response: an individualised approach

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Introduction

Overall, the partial therapeutic success of the major clinical trials of antihypertensive treatment has highlighted some of the limitations of traditional therapeutic policies based upon thiazide diuretics and β -adrenoceptor blockers (Isles *et al.*, 1986; MacMahon *et al.*, 1990). That there is ample scope for improvement has been widely emphasised as new strategies are considered for antihypertensive treatment in the 1990s (Reid, 1988) and one of the new proposals is to attempt a more individualised approach to treatment rather than a strict adherence to pragmatic stepped-care regimens (Menard *et al.*, 1988). Ideally such individualised treatment might involve the following: (1) an initial selection of the most suitable agent (from four or five alternative first-line drugs) based upon readily available clinical and demographic information about the individual, e.g. age, sex, race, lipids and smoking; (2) a rapid assessment, ideally following the first dose of the chosen agent, that the patient is likely to have a satisfactory antihypertensive response without immediate adverse effects; and (3) a judicious selection of the optimum dosage regimen for longterm treatment.

It remains to be established, however, whether or not such prospective treatment regimens, which are intended to suit more closely the requirements of the individual patient, offer significant advantages over conventional practice which is based on a 'trial and error' approach to drug selection with dosage adjustments based upon a retrospective appraisal of the preceding response which is simple to measure. Thus the theoretical basis for optimising and individualising treatment is attractive but the practical problems seem daunting; attempts to predict the most effective drug or an optimum dosage schedule for an individual patient have so far been unsuccessful (Menard *et al.*, 1988).

Individualised treatment approaches have been introduced with some success in other areas of therapeutics, for example with anticonvulsant and bronchodilator drugs, and there is no reason why clinical pharmacokinetic techniques should not be equally applicable to integrate kinetic and dynamic information about antihypertensive therapy in order to guide the choice of drug and dosage regimen and thereby improve not only blood pressure control but also patient tolerance. Thus, there is at least the prospect of improving upon some of the well-recognised shortcomings of 'traditional' antihypertensive treatment; not least in terms of an overall increase in the

magnitude of the blood pressure reduction (more than 6 mm Hg) (MacMahon *et al.*, 1990); the proper provision of 24 h blood pressure control; and the avoidance of dose-concentration-related adverse effects. The application of individualised dosage schedules should therefore have a favourable effect on the overall risk-benefit relationship.

Variability in antihypertensive drug response

It is a statement of the obvious that the magnitude of the response to any drug is dependent upon not only the 'sensitivity' of the individual to the pharmacological effect but also the amount of drug which reaches the site of action. Generally, however, studies of antihypertensive drug response have ignored pharmacokinetic considerations and hence it is no real surprise that remarkably little progress has been made over the last 20 years towards identifying and clarifying which patients (in routine clinical practice) respond best to which drugs. Although wide interindividual variability in plasma drug concentrations and dosage requirements is well recognised with many different antihypertensive agents, previous studies which have investigated the inter and intra subject variability in hypotensive response have usually ignored pharmacokinetic differences and consequently a number of conflicting and often misleading statements have arisen. For example, concerning variations in responsiveness relating to *age* (Bidiville *et al.*, 1988; Buhler *et al.*, 1982; Ferrara *et al.*, 1985; Ram, 1987), to *ethnic origin* (Seedat & Reddy, 1971; Seedat, 1989) and to biochemical parameters, particularly *plasma renin activity* (Bidiville *et al.*, 1988; Buhler *et al.*, 1982; Cody *et al.*, 1983).

A further major problem with many of these studies, which is often underestimated, is that the 'response' to an antihypertensive drug is difficult to define because it is not a discrete and finite end-point. Thus, although blood pressure itself may be readily measurable, identification of a 'successful' response to treatment is difficult to define, it is complicated by the unknown magnitude of 'placebo effects' and it is further compromised if reliance is placed entirely on measurements at a single time point which may represent trough or peak effects, or neither. Thus, an accurate quantitative assessment of antihypertensive drug *response*, and its variability, requires that proper account be taken of several important

factors – measurement of the (placebo-adjusted) reduction in blood pressure, measurement of the underlying plasma drug concentrations, and allowances for time factors. The importance of time factors also has been underestimated since, within each individual, there are variations across the dosage interval in plasma drug concentration and there are underlying circadian changes in the level of blood pressure. In most previous studies antihypertensive response has been quantified on the basis of pharmacodynamics alone – usually single measurements of blood pressure recorded on one or two separate occasions – and no account has been taken of interindividual differences in plasma drug concentration or of time-related variations in blood pressure or pharmacokinetics.

Concentration-effect relationships (and time)

For some drugs there is a simple and direct relationship between the time-course for the drug concentration in plasma and the measured response. Essentially, this implies that there is a rapid equilibration between the drug concentration in plasma and that at the site of action. For many drugs, however, the relationship is not simple and the time-course of drug effect (i.e. the measured response) is out of phase with the plasma drug concentration profile (i.e. delayed). This time lag or temporal discrepancy between concentration and effect may simply reflect the time taken for the drug-receptor interaction to produce its effect; or it may be due to the delayed penetration of drug into a 'deep' tissue compartment; or it may reflect the formation of an active metabolite. Thus, in addition to circadian variability this additional type of time factor needs to be taken into account when characterising the relationship between a continuously changing plasma drug concentration and the corresponding blood pressure response.

For these, and other, reasons it has been suggested that for most antihypertensive drugs no predictable concentration-effect relationship exists. As a result, pharmacokinetic and pharmacodynamic variability have been investigated separately and those studies which have attempted to relate plasma drug concentration to the fall in blood pressure have largely been unsuccessful. An additional confounding factor is that such studies usually have sought correlations between drug concentration and effect data for *groups* of subjects (Biollaz *et al.*, 1982; de Leeuw *et al.*, Kleinbloesem *et al.*, 1987; Larochelle *et al.*, 1982; Lehtonen *et al.*, 1977) and the wide range of inter-subject variability in both kinetic and dynamic parameters has been a significant factor in their failure. Generally, concentration-effect relationships are identified more readily and more consistently when *individual* subjects are considered (Kelman *et al.*, 1983; Pasanisi & Reid, 1983).

In classical pharmacological experiments the concentration-effect relationship is usually depicted by a plot of effect against the log of drug concentration and it typically takes the form of a sigmoid- $E_{\max}$ curve (Figure 1). Thus, there is a clearly defined relationship between concentration and effect but the magnitude of any change in response is related not only to the magnitude of the

Figure 1 The conventional pharmacokinetic model, for example with central (C) and peripheral (P) compartments, is extended to incorporate an additional effect compartment (E). The drug concentration in E (C_e), at each time point, is then related to the corresponding effect (i.e. the placebo-subtracted reduction in blood pressure) but the equation that best characterises this relationship depends upon the portion of the concentration-response curve covered.

change in concentration but also to the portion of the concentration-response curve covered for that drug. It seems highly probable, therefore, that those antihypertensive drugs, particularly β -adrenoceptor blockers and thiazide diuretics, which have long been pronounced to have 'flat' dose-response curves (Hansson *et al.*, 1974; MacGregor *et al.*, 1983) have been administered in relatively high doses which have consistently produced drug concentrations at the top end of the concentration-effect curve and so it has not proved possible to identify clear dose-related effects.

Analysis of concentration-effect relationships

Characterisation of the inter-relationship between the effect of a drug and its concentration in plasma, across a period of time, has been variously called 'concentration-effect analysis' or 'pharmacodynamic modelling' or 'effect modelling' (Whiting & Kelman, 1980).

The fundamental feature of this mathematical approach to integrating kinetic and dynamic time profiles is that the conventional compartmental pharmacokinetic model is extended to incorporate an additional 'effect' compartment, which is constrained to be small enough so as not to perturb the pharmacokinetic parameters defined by the original model (Holford & Sheiner, 1981). The measured effect (i.e. the placebo-subtracted reduction in blood pressure) is then related to the drug concentration in the effect compartment (C_e) at each time point. The concentration-effect relationship in the effect compartment should theoretically be dependent upon a non-

linear (Langmuir, $E_{\max}$) model (equation 1), but within the range of values that are usually obtained in human studies the data may be adequately characterised by a linear model (equation 2):

$$\text{Equation 1} \quad E = \frac{E_{\max} \cdot C_e}{C_{e50} + C_e} \quad (\text{non-linear Hill or Langmuir model})$$

$$\text{Equation 2} \quad E = mC_e + i \quad (\text{linear model})$$

On theoretical grounds, in intact man the relationship between drug concentration and the corresponding response should be described most accurately by an $E_{\max}$ equation (equation 1) where $E_{\max}$ is the theoretical maximum possible effect and C_{e50} the drug concentration required to produce 50% of $E_{\max}$ (Figure 1). In clinical studies, however, where data points are usually collected over a restricted portion of the concentration-response curve (often not attaining even 50% of the theoretical maximum effect), the kinetic-dynamic relationships are often adequately described by the simpler linear model (equation 2) where E is the measured effect, m is the slope of the relationship, i is the intercept and C_e the calculated drug concentration in the effect compartment.

The linear model has the practical advantage that the slope of the relationship (m) represents the effect per unit change in drug concentration and characterises antihypertensive 'responsiveness' in that individual patient in mm Hg per ng ml⁻¹. However, the main limitation of the linear model is its inability to predict the maximum possible drug effect in that individual. The first order rate constant within the effect model (K_{eq}) provides an index of the temporal discrepancy between the time profile for the plasma concentration and the time profile for effect, and has units of h⁻¹ (Figure 1).

Responsiveness to antihypertensive drugs

The numerous potential applications of the technique of concentration-effect analysis have been reviewed extensively elsewhere (Holford & Sheiner, 1981). In recent years this integrated approach has been successfully extended to antihypertensive drugs to characterise relationships between drug concentration and hypotensive response in a series of studies in individual subjects (Donnelly *et al.*, 1988a, 1988b, 1989, 1990a; Elliott *et al.*, 1989; Meredith *et al.*, 1987). This series of clinical studies followed a similar basic design in which pharmacokinetic and pharmacodynamic profiles were measured over 8–10 h for each patient on each study day to evaluate the effects of placebo, first dose administration and steady state (1–6 weeks) treatment. In all of these studies the acute and chronic kinetic-dynamic relationships and the antihypertensive responses were characterised, either by the linear model or the non-linear ($E_{\max}$) model. Concentration-effect relationships were described for each individual in terms of the reduction in systolic as well as diastolic blood pressure and in the case of enalapril parameters were also obtained to characterise the inhibition of plasma ACE activity (Donnelly *et al.*, 1990a). The principal results are summarised in Table 1.

The fundamental advantage of this approach is that the parameters derived from the concentration-effect analysis – either m or $E_{\max}$ and C_{e50} – provide a relatively simple numerical end-result which characterises antihypertensive responsiveness in the individual patient. In particular, this end-result is standardised to take account of inter and intra subject variability in pharmacokinetics, the magnitude of the blood pressure response, placebo effects and time-related changes in blood pressure and drug concentration during the dosage interval.

Table 1 The application of drug concentration-effect analysis to characterise antihypertensive drug responses in individual subjects in terms of a linear or non-linear ($E_{\max}$) model. Published studies in hypertensive patients.

Drug	Concentration-effect model	Reference	Responsiveness (m or $E_{\max}/C_{e50}$) in mmHg per ng ml ⁻¹ ± s.d.	
			Acute	Chronic
i) Calcium antagonists				
Verapamil	linear	Donnelly <i>et al.</i> (1988a)	-0.13 ± 0.06	-0.12 ± 0.06
Nifedipine	linear	Meredith <i>et al.</i> (1987)	-0.48 ± 0.2	-0.49 ± 0.2
ii) α_1 -adrenoceptor antagonists				
Prazosin	linear	Elliott <i>et al.</i> (1989)	-11.5 ± 6.7	-8.5 ± 5.0*
Doxazosin	linear	Donnelly <i>et al.</i> (1989)	-2.1 ± 0.8	-1.4 ± 0.8*
iii) ACE inhibitors				
Enalapril	E _{max}	Donnelly <i>et al.</i> (1990a)	-0.64 ± 0.3	-0.96 ± 1.4
iv) β -adrenoceptor blockers				
Dilevalol	E _{max}	Macphee <i>et al.</i> (1991)	-3.5 ± 3.0	-2.1 ± 1.3

* significant difference between acute and chronic.

Having derived a mathematical index which is reproducible and which takes account of the fundamental factors that contribute to the variability in antihypertensive response it is then possible to investigate extrinsic factors, for example:

- The constancy and predictability of the long-term blood pressure response to antihypertensive drugs.
- Factors which influence the magnitude of the response (determinants of response – e.g. plasma renin activity, age, starting blood pressure).

Constancy and predictability of the long term response

Calcium antagonists The concentration-effect relationships for both nifedipine and verapamil have been found to be characterised most appropriately by the linear model (Donnelly *et al.*, 1988a; Meredith *et al.*, 1987). The fitted profile of the modelled antihypertensive response to nifedipine in a representative patient is shown in Figure 2. To assess the constancy of the concentration-effect relationship within each individual comparisons were made of the responsiveness (in mm Hg per ng ml⁻¹) calculated following the first dose (acute) with that calculated during steady state therapy (Table 1). There were significant correlations between acute and chronic responsiveness (nifedipine, $r = 0.78$; verapamil, $r = 0.90$) and the slopes of these relationships were not significantly different from unity (Donnelly *et al.*, 1988a; Meredith *et al.*, 1987).

The constancy of the acute and chronic antihypertensive effects defined in these studies for nifedipine and verapamil is at variance with the isolated report that the antihypertensive effect of nisoldipine may diminish with time perhaps due to 'tolerance' (Waller & Ramsay, 1987). However, clear confirmation of such tolerance, which may reflect either an adaptation of pharmacodynamic mechanisms or changes in underlying pharmacokinetics and drug disposition, requires a comparative analysis of the blood pressure reduction per unit of drug concentration during the period of treatment. In these detailed studies with nifedipine and verapamil there was

no suggestion of tolerance since the fall in blood pressure per unit drug concentration was the same at 1 week and 6 weeks compared with first dose administration.

α -adrenoceptor blockers As with the calcium antagonists, the concentration-effect relationships for both prazosin and doxazosin were described most appropriately by a linear model (Donnelly *et al.*, 1989; Elliott *et al.*, 1989) and there were significant correlations between acute and chronic responsiveness (e.g. $r = 0.63$ doxazosin). However, the slopes of both relationships were significantly less than unity and there was a significant, but consistent, reduction (of approximately 30%) in the responsiveness during chronic treatment compared with first dose administration (Table 1).

Tolerance to the α -adrenoceptor blocking effect of prazosin has been well documented in cardiac failure (Desch *et al.*, 1979) and there is evidence that adaptive changes in α -adrenoceptor-mediated responses occur within a few days (von Bahr *et al.*, 1982). The results of the concentration-effect studies indicate, however, that the attenuation in antihypertensive responsiveness to doxazosin and prazosin occurs early (within the first few days or so) and is not thereafter progressive, since there was no change in responsiveness between 1 and 6 weeks (Donnelly *et al.*, 1989).

β -adrenoceptor antagonist drugs To date, investigation of individual responses to acute and chronic treatment with a β -adrenoceptor blocker type of drug has been undertaken only with diltiazem (Macphie *et al.*, 1991). An $E_{\max}$ -model was found to be most appropriate for the concentration-effect relationship but again there was a significant correlation between acute and chronic responsiveness (either as $E_{\max}$ or as C_{e50}) ($r = 0.81$) with a slope not significantly different from unity.

ACE inhibitors In terms of characterising antihypertensive response, the pharmacokinetic features of ACE inhibitor drugs add an additional complexity. It is now well recognised that these drugs do not show conventional and dose-linear characteristics (Till *et al.*, 1984) and so a different underlying pharmacokinetic model is required. Models based on the putative saturable binding of the drug to both tissue and circulating angiotensin converting enzyme (i.e. a protein-binding type of model) have been shown to be most appropriate for pharmacokinetic characterisation (Francis *et al.*, 1987; Lees *et al.*, 1989). Furthermore, similar to the finding with β -adrenoceptor blockers, the linear model was found to be inadequate to characterise the effect relationship with enalaprilat and an $E_{\max}$ function was required (Donnelly *et al.*, 1990a). Similar $E_{\max}$ responses have been reported with other ACE inhibitors (Francis *et al.*, 1987; Kelman *et al.*, 1983) and this may partly explain why ACE inhibitor drugs also have been reported to have shallow or flat dose-response curves (Davies *et al.*, 1984; Gomez *et al.*, 1985), reflecting the use of relatively high doses producing drug concentrations towards the top end of the concentration-effect curve.

Thus, blood pressure reduction and ACE inhibition were characterised using the Langmuir- $E_{\max}$ relationship and again there was a significant correlation between acute and chronic responsiveness ($r = 0.74$) with a slope

Figure 2 The broken line ($\triangle - - - \triangle$) represents the effect profile predicted by a linear model on the basis of kinetic information alone (and assuming a linear relationship between E and C_e). The modelled profile is in close agreement (i.e. well fitted) to the actual blood pressure response ($\blacktriangle - \blacktriangle$) and the derived responsiveness (m) to a single dose of nifedipine for that individual is $-0.43 \text{ mm Hg ng}^{-1} \text{ ml}^{-1}$ (Donnelly *et al.*, 1988a).

which did not differ significantly from unity (Donnelly *et al.*, 1990a).

Summary The results of these studies with different classes of antihypertensive drug indicate that chronic antihypertensive responsiveness is correlated with acute responsiveness. This suggests that the adequacy of the long-term response to treatment may be identified prospectively by an appropriate analysis of the kinetic and dynamic parameters associated with the first dose response.

Determinants of response

The possibility of prospectively identifying 'responders' and 'non-responders' on the basis of simple baseline characteristics has been the focus of much research. Plasma renin activity has been of particular interest and other factors such as age and ethnic origin (and their inter-relationships with plasma renin activity) have also been much investigated but, as discussed earlier, almost no account has been taken of interindividual variability in pharmacokinetics. However, there is accumulating evidence to suggest that the importance of the achieved plasma drug concentration has been significantly underestimated. For example, in an analysis of more than 60 patients, receiving a variety of antihypertensive agents, differences in plasma drug concentration accounted for most (> 80%) of the variability in antihypertensive response (Donnelly *et al.*, 1991); this applied to both acute and chronic dosing and included not only the inter-subject variability but also the intra-subject variability during a dosage interval and over a treatment period of 6 weeks.

Since age or ethnic origin may affect the magnitude of the antihypertensive effect by influencing pharmacokinetics, independently of any influence on pharmacodynamics, it seems more appropriate to seek information about 'determinants of response' by employing an integrated kinetic-dynamic approach. Thus, having standardised for drug concentration, other factors which may influence antihypertensive response, such as age and plasma renin activity, can be assessed more clearly.

The data from the studies listed in Table 1 have been analysed by stepwise multiple linear regression analysis to evaluate other factors which contribute significantly to the variability in antihypertensive responsiveness (Donnelly *et al.*, 1991). Thus, with this approach responsiveness (m or $E_{\max}$) is the dependent variable and several major independent variables (such as plasma renin activity, age, starting blood pressure and the first dose response) are modelled separately and in combination by fitting a hierarchy of linear models to find the best fit. The r^2 value (the coefficient of variation) obtained for each model represents the percentage variability in responsiveness which can be accounted for by each independent variable or combination of variables in the model.

Plasma renin activity Alterations to sodium intake and correspondingly differences in plasma renin activity have been shown to influence the response to antihypertensive drugs, such as ACE inhibitors (Gavras *et al.*, 1978), calcium antagonists (Erne *et al.*, 1983) and β -adreno-

ceptor blockers. However, there remains considerable dispute about the importance of plasma renin activity (PRA) as a predictive marker of blood pressure response in routine clinical practice since PRA generally covers a narrow range in uncomplicated salt replete patients with mild-to-moderate essential hypertension (Cody *et al.*, 1983).

From our multiple regression analysis pretreatment PRA accounted for considerably less than 10% of the variability in response to treatment (Donnelly *et al.*, 1990b).

Age There have been conflicting reports about the effect of age on antihypertensive drug response. For example, widely different conclusions have been reached about the relationship between age and the antihypertensive effect of calcium antagonists (Buhler *et al.*, 1982; Ferrara *et al.*, 1985; Ram *et al.*, 1987). Age affects pharmacokinetic as well as pharmacodynamic responses (Lees & Reid, 1987; Robertson *et al.*, 1988) but previous studies have addressed the kinetic and dynamic variability separately. Thus, although the fall in blood pressure with verapamil was greater in the elderly (Buhler *et al.*, 1982), this does not exclude the possibility of higher drug levels (rather than genuinely increased responsiveness) in older patients.

In our multiple regression analysis, having corrected for possible age-related differences in plasma drug concentration, age accounted for less than 12% of the variability in responsiveness to calcium antagonists and enalapril (Donnelly *et al.*, 1990b, 1991).

Starting blood pressure The relationship between starting blood pressure and antihypertensive response has been considered in detail elsewhere (Sumner *et al.*, 1988). To define the full extent of this relationship over a wide range of blood pressures often requires data from normotensive as well as hypertensive subjects, as illustrated for verapamil and enalapril in Figure 3 (Meredith *et al.*, 1987).

For all drugs in this multiple regression analysis there were significant positive correlations between responsiveness and starting (pretreatment) blood pressure. This relationship was more consistent with systolic than with diastolic blood pressure and for enalapril, prazosin and verapamil produced the best prediction of response to the first dose (accounting for 48%, 64% and 65% of the variability in m or $E_{\max}$, respectively) such that incorporating additional independent variables, such as age and plasma renin activity did not significantly improve the correlation.

First dose response It has been claimed that the variability in antihypertensive response between and within individuals is sufficiently erratic and unpredictable that it represents a major obstacle to the prospective optimisation of drug treatment regimens (Menard *et al.*, 1988). For example, there are reports that the first dose response to an ACE inhibitor (or calcium antagonist) bears no relationship to the response obtained during long-term treatment (Bidiville *et al.*, 1988) and that it takes several weeks to achieve maximal blood pressure 'response' to both captopril and enalapril (Brunner *et al.*, 1983; Laragh *et al.*, 1980). However, as mentioned earlier, it is difficult

Figure 3 Relationships between 'responsiveness' and pretreatment blood pressure over a wide range of blood pressure data from hypertensive patients (■) and normal volunteers (□) for verapamil and enalapril (Meredith *et al.*, 1989).

to draw firm conclusions about the constancy of drug response from pharmacodynamic information alone and it is probably more appropriate to evaluate the predictability of response in individuals rather than for groups of subjects.

The determinants of response during long term treatment have been examined using acute responsiveness (i.e. m or E_{max}) as an independent variable. Overall, having allowed for differences in underlying drug concentration, the magnitude of the response to the first dose and the height of the pretreatment blood pressure emerge as the two most important factors that determine the response to chronic therapy (Donnelly *et al.*, 1990b, 1991).

A prospective individualised approach to antihypertensive treatment

These concentration-effect studies have demonstrated that it is possible to investigate the constancy of drug response and identify close correlations between the response to the first dose and the response obtained after 4–6 weeks following a number of different antihypertensive agents. This constancy of antihypertensive responsiveness has been further explored by using the kinetic and dynamic parameters derived after the first dose to predict the blood pressure profiles during chronic treatment, for individual patients (Figure 4; Meredith *et*

Figure 4 The blood pressure response during chronic treatment with enalapril can be predicted from the first dose parameters. The solid lines represent the blood pressure profiles at steady state (placebo-corrected) that have been predicted from the model by an appropriate analysis of the kinetic and dynamic information from the *first dose*, and the individual points (●) show the actual blood pressure profile after 6 weeks treatment. These three individuals illustrate the inter-subject variability in peak to trough responses with a standard once daily regimen of 20 mg.

al., 1989, 1990). Clearly this has potential clinical application in that the response to the first dose, for an individual patient, may be used to forecast the response during long-term treatment and thereby allow prompt identification of poor or non-responders. Not only is there scope to predict the response to a fixed dosage regimen and to identify an individual dosage requirement but there is also scope to investigate, by simulation, the response profiles for a range of alternative dosage schedules, e.g. once or twice daily administration. Thus, there is the real prospect of developing a rational basis for choosing the optimum dose for individual patients (Meredith *et al.*, 1990).

Clearly, therefore, concentration-effect analysis has potential clinical utility for optimising long-term antihypertensive therapy, provided that there is relevant *a priori* knowledge about non-linear pharmacokinetics and E_{max} concentration-effect relationships, etc. However, for concentration-effect analysis to become part of routine clinical practice it requires that the procedure for characterising responsiveness in each

individual patient is practicable and straightforward using a small number of selected measurements of blood pressure and plasma drug concentration. This will depend upon further improvements in analytical techniques and the application of population pharmacokinetic analysis whereby one or two measurements per individual can be interpreted in relation to the database derived from a reference population and the pharmacokinetic and concentration-effect parameters predicted with reasonable confidence.

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